Diagnosis and Management of Precancer of Endometrium

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Question 1

ACOG/SGO preferred terminology for precancer of endometrium is:

1. Premalignant endometrial lesion.
2. Endometrial intraepithelial neoplasia.
3. Atypical endometrial hyperplasia.
ACOG/SGO recommended sampling of endometrium is:

2. Endometrial biopsy with suction curette.
3. Hysteroscopy directed D&C.
4. Hysterectomy.
Epidemiology of endometrial Ca

• 4\textsuperscript{th} most common cancer in women
• 7\textsuperscript{th} leading cause of death among female malignancies
• 54,870 new cases/ 10,170 deaths in the US 2015
• 2.81 % lifetime risk- white, 2.48%- black
• 0.5% lifetime mortality risk among American women
• >70% of cases are Stage 1: 90% 5-year survival
Background

• Endometrial hyperplasia is a precursor lesion of endometrial adenocarcinoma
• Precursor lesion of Type 1 endometrial adenocarcinoma is

**Endometrial Intraepithelial Neoplasia**

• Endometrial hyperplasia
  – Estrogenic stimulation of endometrium
  – Unopposed by progestins/ prolonged
  – Biologically distinct from true precancerous lesion or true neoplasm
Objectives of Classification for Premalignant Lesions of Endometrium

• Criteria and terminology clearly distinguish between hyperplasia and true pre-cancer.
• Managed differently due to their different cancer risk.
• Matched with appropriate intervention to avoid under- or overtreatment.
Two systems of endometrial precancer nomenclature in use

• WHO94 schema
  – Older.
  – Most commonly used by pathologists.

• Endometrial Intraepithelial neoplasia diagnostic schema
  – Developed by International Endometrial Collaborative Group
WHO94 schema

• Classifies histology based on glandular complexity and nuclear atypia
• Four categories of risks stratifications
  1. Simple hyperplasia
  2. Complex hyperplasia
  3. Simple hyperplasia with atypia
  4. Complex hyperplasia with atypia
WHO94 schema

- Kurman data
  1. Simple hyperplasia 1%
  2. Complex hyperplasia 3%
  3. Simple hyperplasia with atypia 9%
  4. Complex hyperplasia with atypia 29%

- GOG 167 data

  Trimble and Zaine

  43% of women with endometrial biopsy of Atypical Complex Hyperplasia have underlying invasive endometrial carcinoma at hysterectomy
WHO94 schema- Issues

• Categories are descriptive in nature.
• Interpretation is subjective.
• Poor reproducibility of the individual case classification
• Individual categories do not suggest specific management algorithm
• Lacking benefit to clinical management
Endometrial Intraepithelial Neoplasia schema

• Precancer is termed “Endometrial Intraepithelial Neoplasia”
• Diagnosis used by EIN schema
  – Disease specific classification
  – Informs clinical management
• Confirmed as prognostic by published data
  – Baak et al. Cancer 2005
  – Mutter et al. Hum Pathol 2008
  – Hecht et al. Mod Pathol 2005
• Greater inter-observer reproducibility that with the WHO94 schema
## Diagnostic Criteria for Endometrial Intraepithelial Neoplasia*

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Topography</th>
<th>Functional Category</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign endometrial hyperplasia</td>
<td>Diffuse</td>
<td>Prolonged estrogen effect</td>
<td>Hormonal therapy, symptomatic</td>
</tr>
<tr>
<td>Endometrial intraepithelial neoplasia</td>
<td>Focal progressing to diffuse</td>
<td>Precancerous</td>
<td>Hormonal therapy or surgery</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma, endometrioid type, well differentiated</td>
<td>Focal progressing to diffuse</td>
<td>Malignant</td>
<td>Surgery, stage based</td>
</tr>
</tbody>
</table>

*Previously known as atypical endometrial hyperplasia.
**Definition of Endometrial Intraepithelial Neoplasia Criteria**

<table>
<thead>
<tr>
<th>Endometrial Intraepithelia Neoplasia* Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Area of glands greater than stroma (volume percentage stroma less than 55%)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytology differs between architecturally crowded focus and background</td>
</tr>
<tr>
<td>Size greater than 1 mm</td>
<td>Maximum linear dimension exceeds 1 mm</td>
</tr>
<tr>
<td>Exclude mimics</td>
<td>Benign conditions with overlapping criteria (ie, basalis, secretory, polyps, repair)</td>
</tr>
<tr>
<td>Exclude cancer</td>
<td>Carcinoma if maze–like glands, solid areas, or appreciable cribriforming</td>
</tr>
</tbody>
</table>

*Previously known as atypical endometrial hyperplasia.
Precancer Diagnosis

• Sensitive and Specific
• Exclusion of preexisting carcinoma
• Endometrial Sampling
  – Problem with suction curette: 43% of cancer at hysterectomy;
  – D&C: samples less than 60% of uterine cavity
  – Method is less important if hysterectomy is planned
Endometrial sampling

- D&C to diagnose Endometrial Intraepithelial Neoplasia is less likely to miss cancer than suction curettage: 27% vs 46%  
  - Mass lesion may impinge uterine cavity and deflect Pipelle

- Hysteroscopy with direct biopsy is more sensitive than D&C

- Current diagnostic schema should include an assessment of sample adequacy
  - As of cervical cytology specimen
  - Include any discrete lesions as well as background endometrium

Leitao et al. Am J Obstet Gynecol 2010
Bedner et al. Eur J Gynaecol Oncol 2007
Diagnosis of Endometrial Cancer among women with PMB

- **Transvaginal Ultrasound**
  - Excellent Negative Predictive Value
  - Should be limited to postmenopausal women with PMB

- **Assessment of endometrial thickness**
  - 4 mm or less: no EMB is required due to low risk of malignancy.  
    - Greater than 4 mm: Alternative evaluation
    - Sonohysterogram, Hysteroscopy...
  - Significance of greater than 4 mm in asymptomatic, postmenopausal woman has not been well established
    - No routine evaluation is needed

*ACOG Committee Opinion No. 440. 2009*
Management of Endometrial Intraepithelial Neoplasia

• Objectives
  – Rule out concurrent adenocarcinoma;
  – Design a treatment plan that can accommodate delayed discovery of occult malignancy
  – Prevention of progression of endometrial cancer
Management of Endometrial Intraepithelial Neoplasia

• Non-surgical management
  – Not as well defined

• Total hysterectomy
  – Effective means of treating premalignant lesion
Non-surgical management

- Acceptable for patients
  - Desire future fertility
    - Goal: complete clearance of disease, reversion to normal endometrial function, prevention of cancer
  - Medical comorbidities precluding surgery
    - Goal: disease stabilization, reduction of rate of endometrial cancer, conversion to chronic medical management
# Progestin management of Endometrial Intraepithelial Neoplasia

<table>
<thead>
<tr>
<th>Hormonal Agent</th>
<th>Dosage and Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>10–20 mg/d, or cyclic 12–14 days per month</td>
</tr>
<tr>
<td>Depot medroxyprogesterone</td>
<td>150 mg intramuscularly, every 3 months</td>
</tr>
<tr>
<td>Micronized vaginal progesterone</td>
<td>100–200 mg/d or cyclic 12–14 days per month</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>40–200 mg/d</td>
</tr>
<tr>
<td>Levonorgestrel intrauterine system</td>
<td>52 mg in a steroid reservoir over 5 years</td>
</tr>
</tbody>
</table>
Progestin management of Endometrial Intraepithelial Neoplasia

• Regression rate
  – Most studies of small sample size
    • Levonorgestrel IUD- up to 90% overall but 67% with atypia;
    – Systematic review and meta-analysis of 14 studies
      69% (95% CI 0.58-0.93) for atypical hyperplasia

• Follow up
  – Total hysterectomy is ideal
  – Serial endometrial sampling every 3-6 months
Progestin management of Endometrial Intraepithelial Neoplasia

- Risks – proper assessment and counseling
  - Edema
  - GI disturbances
  - Thromboembolic events
Progestin management of Endometrial Intraepithelial Neoplasia

• Recurrence
  – Underlying hormonal cause remains after therapy is completed
  – Recurrence is possible if treatment is not continued indefinitely

– Obesity
  • Weight loss
  • Bariatric surgery
Surgical management of Endometrial Intraepithelial Neoplasia

• Total hysterectomy
  – Definitive assessment of for occult carcinoma
  – Includes abdominal, vaginal and MIS procedures
  – Acceptable with and without BSO

• Unacceptable methods
  – Supracervical hysterectomy, morcellation and endometrial ablation
  – Concerns of underlying carcinoma

*Supracervical hysterectomy. ACOG Committee Opinion No. 388. 2007*
Surgical management of Endometrial Intraepithelial Neoplasia

• Cervix and lower uterine segment should be removed
• Uterine morcellation is contraindicated to women with suspected uterine malignancy
• All patients should be informed of the possibility to undergo additional staging surgery
Surgical management of Endometrial Intraepithelial Neoplasia

- Intraoperative assessment
  - Frozen section
    - High risk disease is identified more frequently
    - Correlation between frozen section and final report for histology, grade and depth of invasion is 97.5/88/98.2%
      
      \[ \text{Stephan et al. Gynecol Oncol 2014} \]

  - Opening the specimen in the OR
    - Gross evidence of tumor
    - Myometrial invasion

  - If gyn/oncologist is not available immediately
    - Reasonable to wait for final pathology
Risk of malignancy

• GOG 167
  – 43% of women with Atypical Complex Hyperplasia have underlying invasive endometrial carcinoma at hysterectomy
Comprehensive surgical staging

- Risk of concurrent high risk malignancy is 10%  
  \textit{AlHilli et al. Gynecol Oncol 2013}
- Large majority would not benefit from pelvic and paraaortic lymphadenectomy
- Total hysterectomy with or without BSO is the most appropriate surgical treatment for Endometrial Intraepithelial Neoplasia with additional staging involving gyn/onc
- Issues with vaginal hysterectomy
Considerations for Lynch syndrome

• Autosomal-dominant syndrome
• Defect in DNA mismatch repair genes
  – MLH1, MSH2, MSH6, and PMS2
• Risk of colon cancer- 70% by age of 70
  \[\text{JAMA 2006;296: 1507-17}\]
• Risk of uterine cancer- 16-61%
• Risk of ovarian cancer- 5-10%
• Risk of urinary tract, hepatobilliary, intestinal malignancies
Considerations for Lynch syndrome

• Only 3-5% of all uterine cancer attributable to Lynch syndrome
• Women younger than 50 years
  – 5–9% of women with endometrial cancer will have a detectable deleterious mismatch repair gene mutation
• No evidence of association with aggressive histologic subtypes or worse prognosis
Testing for Lynch syndrome

• Direct germline DNA testing
  – The absence of a deleterious mutation does not exclude Lynch syndrome

• Tumor testing using immunohistochemistry or microsatellite instability testing
  – At this time this approach is utilized by most medical centers
The 2004 Bethesda Guidelines (Modified to Include Endometrial Cancer)

- Patients with endometrial cancer diagnosed before age 50 years
- Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch-associated tumor at any age
- Patients with colorectal cancer with tumor-infiltrating lymphocytes, peritumoral lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern diagnosed before age 60 years
- Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch-associated tumor diagnosed before age 50 years
- Patients with colorectal or endometrial cancer diagnosed at any age with two or more first-degree or second-degree relatives† with Lynch-associated tumors, regardless of age
Key ACOG Publications

• Practice Bulletin 147, November 2014
  “Lynch syndrome”
• Practice Bulletin 149, April 2015:
  “Endometrial cancer”
• Committee Opinion 631, May 2015
  “Endometrial Intraepithelial Neoplasia”
• Committee Opinion 634, June 2015
  “Hereditary Cancer Syndromes and Risks Assessment”